

REMARKS

Reconsideration and withdrawal of the rejections of this application and consideration and entry of this paper are respectfully requested in view of the herein remarks and accompanying information, which place the application in condition for allowance.

I. Status of Claims and Formal Matters

Claims 1, 3-9, 13-17, 28-32, 45-48, 50-51, 54-62, 66-69, 93, and 95-96 are currently pending in the present application. Claim 1 was amended to add the recitation, “comprising a full-length lineage I WNV cDNA clone.” Claim 4 was amended to recite, “A reverse genetics system for screening and identifying antilaviviral compounds comprising a lineage I WNV replicon. Claims 5, 46, 60 and 95 were amended for clarity. Claim 95 was further amended to eliminated reference to SEQ ID NO:1. Claims 3, 10-12, 20-21, and 96 are canceled herein.

No new matter is added.

The Examiner is thanked for rejoining the cDNA clone and replicon species. The Examiner is thanked for withdrawing the rejection of claims 1, 32, 59, 61, 62, and 66 under 35 U.S.C. §103 as being unpatentable over Shi in view of Hicks. The Examiner is thanked for withdrawing the rejection of claims 67, 68, and 69 under 35 U.S.C. §103 as being unpatentable over Shi in view of Hicks in view of Khromykh. The Examiner is thanked for withdrawing the rejection of claims 1, 32, 45, 50, 51, 54, 55, 57, and 93 under 35 U.S.C. §103 as being unpatentable over Khromykh in view of Chambers supported by Barrett. The Examiner is thanked for withdrawing the rejection of claims 47, 48, 56, and 58 under 35 U.S.C. §103 as being unpatentable over Khromykh and Chambers supported by Barrett in view of Hicks. The Examiner is thanked for withdrawing the rejection of claims 1, 32, and 59 under 35 U.S.C. §103 as being unpatentable over Hurrelbrink in view of Chambers supported by Barrett. The Examiner is thanked for withdrawing the rejection of claims 61, 62, and 66 under 35 U.S.C. §103 as being unpatentable over Hurrelbrink and Chambers supported by Barrett in view of Hicks. The Examiner is thanked for withdrawing the rejection of claims 67, 68, and 69 under 35 U.S.C. §103 as being unpatentable over Hurrelbrink and Chambers supported by Barrett and Hicks in view of Khromykh.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited in the Office Action, and that these claims are in full compliance with the requirements of 35 U.S.C. §112. The amendments to the claims, as presented herein,

are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103, or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

II. The Objections Under 35 U.S.C. § 102 Are Overcome

Claim 1 is rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Chambers *et al.* The Examiner asserts that Chambers *et al.* teaches the use of reverse genetics systems to create chimeric flaviviruses that can induce neutralizing antibodies and be used for screening and identifying antinflaviviral compounds. Claim 1 is also rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Lai *et al.* The Examiner asserts that Lai *et al.* teaches reverse genetics systems and attenuated backbones to construct chimeric flaviviruses for DEN-4 that can be used in screening and identifying antinflaviviral compounds. Claim 1 is also rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Yamshchikov *et al.* The Examiner asserts that Yamshchikov *et al.* teaches reverse genetic systems and a replicon of WNV that can be used in screening and identifying antinflaviviral compounds. Applicants respectfully disagree and traverse the rejection.

It is respectfully pointed out that a two-prong inquiry must be satisfied in order for a Section 102 rejection to stand. First, the prior art reference must contain all of the elements of the claimed invention. *See Lewmar Marine Inc. v. Bariant Inc.*, 3 U.S.P.Q.2d 1766 (Fed. Cir. 1987). Second, the prior art must contain an enabling disclosure. *See Chester v. Miller*, 15 U.S.P.Q.2d 1333, 1336 (Fed. Cir. 1990). A reference contains an enabling disclosure if a person of ordinary skill in the art could have combined the description of the invention in the prior art reference with his own knowledge of the art to have placed himself in possession of the invention. *See In re Donohue*, 226, U.S.P.Q. 619, 621 (Fed. Cir. 1985).

Applying the law to the instant facts, the references relied upon by the Office Action do not disclose, suggest or enable Applicants' invention.

Claim 1 has been amended herein to recite, "A reverse genetics system for screening and identifying antinflaviviral compounds comprising a full-length lineage I WNV cDNA clone." Chambers involves construction of **chimeric yellow fever/Japanese encephalitis (YF/JE)** viruses from cDNA templates encoding various structural proteins. Lai involves the construction of **dengue type 4 virus** cDNA, yielding infectious RNA transcripts, to provide a new approach to the development of safe and effective dengue vaccines. Yamshchikov involves a full-length

infectious clone of the *lineage II WN strain* used to investigate effects of insertion of 5'-end and 3'-end nonrelated sequences on virus replication and infectivity of synthetic RNA. Contrary to the assertions in the Office Action, none of the cited references teach or suggest a reverse genetics system for screening and identifying antiviral compounds comprising a full-length *lineage I WNV* cDNA clone. In fact, Chambers and Lai involve entirely different species of Flavivirus. Yamshchikov, on the other hand, although involving the same species of Flavivirus, relates to *lineage II WNV*. Although lineage I WNV and lineage II WNV are related, the genomes differ significantly. Berthet (copy enclosed, see page 2294, last line to page 2295) reported in 1997, before the filing date of the present invention, that the "nucleotide sequences of virus subtypes in one lineage differed by a maximum of 29% from those of subtypes in the second lineage. Within lineage I the maximum identity of WN strains was 87% and within lineage II it was 80.5%." Therefore, because neither Chambers, Lai, nor Yamshchikov teach or suggest the reverse genetics system for screening and identifying antiviral compounds comprising a full-length lineage I WNV cDNA clone of claim 1, the present invention is not anticipated by the references.

Accordingly, reconsideration and withdrawal of the rejection of claim 1 under 35 U.S.C. §102 is respectfully requested.

III. The Rejections Under 35 U.S.C. §112 Are Overcome

Claims 46, 60, 95, and 96 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In particular, the Office Action alleges that claims 46, 60, 95, and 96 recite wherein the clones and genome are "according" to SEQ ID NO:2, and that it is not clear what the Applicant intends for the relationship between the clones and genome and SEQ ID NO:2 to be: comprising, consisting of, homologous, or having a certain percent identity to the sequence, or nucleotide by nucleotide correspondence with the entire sequence. The rejections are respectfully traversed.

Claim 46 has been amended to recite, "The DNA molecule according to claim 45, wherein said lineage I WNV nucleotide sequence is as set forth in SEQ ID NO.2." Claim 60 has been amended to recite, "The DNA molecule according to claim 59, wherein said lineage I WNV nucleotide sequence is as set forth in SEQ ID NO.2." Claim 95 has been amended to recite, "The reverse genetics system of claim 3, wherein the full-length lineage I WNV cDNA clone is

according to the nucleotide sequence as set forth in-SEQ ID NO:2.” Claim 96 has been cancelled thereby obviating the rejection in part. It is believed the amendments to claims 46, 60, and 95 add clarity and obviate the rejection.

Accordingly, reconsideration and withdrawal of the rejection of claims 46, 60, 95, and 96 under 35 U.S.C. §112 are respectfully requested.

IV. The Rejections Under 35 U.S.C. § 103 Are Overcome

Claims 1, 3, 5, 7, 13, 14, 16, 32, 59, 61, 62, and 66 are rejected under 35 U.S.C. §103(a) as being unpatentable over Hurrelbrink, Xiang, Puri, Yamshchikov and Mishin. Claims 1, 3, 5, 7, 8, 13, 14, 15, 16, 28, 32, 59, 61, 62, 66, 67, 68, and 69 are rejected under 35 U.S.C. §103(a) as being unpatentable over Hurrelbrink, Xiang, Puri, Yamshchikov, and Mishin in further view of Zhu. Claims 1, 3, 5, 7, 8, 13, 14, 15, 16, 28, 30, 31, 32, 59, 61, 62, 66, 67, 68, and 69 are rejected under 35 U.S.C. §103(a) as being unpatentable over Hurrelbrink, Xiang, Puri, Yamshchikov, and Mishin in view of Zhu, further in view of Varnavski. Claims 45, 47, 48, 50, 51, 54, 55, 56, 57, 58, and 93 are rejected under 35 U.S.C. §103(a) as being unpatentable over Chambers supported by Barrett in view of Hurrelbrink, Xiang, Puri, Friebe, Yamshchikov and Mishin, in view of Zhu. Claims 1, 4, 6, 7, 13, 14, 17, 30, and 31 are rejected under 35 U.S.C. §103(a) as being unpatentable over Varnavski in view of Pang, Khromykh, Friebe, and Yamschikov. Claims 1, 4, 6, 7, 9, 13, 14, 15, 17, 29, 30, and 31 are rejected under 35 U.S.C. §103(a) as being unpatentable over Varnavski in view of Pang, Khromykh, Friebe, and Yamschikov in further view of Zhu.

The rejections will be addressed collectively and are respectfully traversed. None of these documents either alone or in any combination teach, suggest, disclose or enable the instantly claimed invention.

The present invention relates to a reverse genetics system for screening and identifying antiviral compounds comprising a full-length lineage I WNV cDNA clone, and to plasmids and DNA molecules relating to full-length lineage I WNV cDNA.

It is respectfully submitted that it is well-settled that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowicz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further still, “obvious to try” is not the standard under 35 U.S.C. §103. *In re Fine*, 5 U.S.P.Q. 2d 1596, 1599 (Fed. Cir. 1988). And, as stated by the Court

in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): “The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification.” Also, the Examiner is respectfully reminded that for the Section 103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Furthermore, it has recently been reaffirmed by the Supreme Court in *KSR* that the factors set out in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18: “[T]he scope and content of the prior art are determined; differences between the prior art and the claims at issue are...ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.” *KSR International Co. v. Teleflex Inc.*, 550 U.S. ____ (2007).

The Office Action alleges that Hurrelbrink teaches full length cDNA of a flavivirus (here, MVE) as well as inclusion of a T7 promoter as well as the use of immunofluorescence assays for detection. Although Hurrelbrink does not teach the lineage I WNV or inclusion of a reporter gene, the Office Action asserts that Xiang teaches full length flavivirus Hepatitis G cDNA; Puri teaches full length flavivirus Dengue cDNA clone, Yamschikov teaches full length flavivirus WNV lineage II cDNA; Mishin teaches another flavivirus (JEV) full length cDNA as well as use of reporter gene (luciferase) to detect expression. The Office Action asserts that one of skill in the art at the time the invention was made would have been motivated to construct a full length WN lineage I cDNA with a reporter gene because Hurrelbrink, Xiang, Puri, Friebe, and Mishin all teach construction of flavivirus infectious full length cDNA (Yamshchikov further teaching full length WN cDNA), thus, it would have been obvious to one of ordinary skill in the art to create a cDNA clone for WNV lineage I as well; and Mishin teaches that incorporation of the reporter gene connotes expression, a functional equivalent for detection of expression. Moreover, the Office Action asserts that one of skill in the art at the time the invention was made would have had a reasonable expectation of success to construct a full length WN lineage I cDNA with a reporter gene because Hurrelbrink, Xiang, Puri, Friebe, and Mishin all teach flavivirus infectious full length cDNA and detection.

The Office Action further alleges that Hurrelbrink, Xiang, Puri, Yamshchikov, and Mishin do not teach a second reporter further comprising an IRES. Zhu teaches plasmids comprising dual reporter systems comprising IRES linking two GFPs for improved detection and process monitoring for cells transfected with complex constructs. The Office Action further asserts that one of skill in the art at the time the invention was made would have had a reasonable expectation of success for using the construct of Hurrelbrink Xiang, Puri, Yamshchikov, and Mishin with the dual GFP/IRES system of Zhu because Zhu teaches enhanced detection for constructs transfected into cells. The Office Action further alleges that one of ordinary skill in the art would have had a reasonable expectation of success for using the construct of Hurrelbrink, Xiang, Puri, Yamshchikov, and Mishin with the dual GFP/IRES system of Zhu because Hurrelbrink, Xiang, Puri, Yamshchikov, and Mishin teach expression of constructs in cells.

The Office Action further alleges that although Hurrelbrink, Xiang, Puri, Yamshchikov, and Mishin in view of Zhu do not teach incorporation of an autoprotease 2a sequence, Varnavski teaches a unique site comprising 2a autoprotease of FMD in order to improve cleavage and expression of heterologous genes including GFPs. The Office Action further alleges that one of skill in the art would have been motivated to combine the construct of Hurrelbrink, Xiang, Puri, Yamshchikov, and Mishin in view of Zhu with the autoprotease of Varnavski because both Hurrelbrink, Xiang, Puri, Yamshchikov, and Mishin in view of Zhu and the autoprotease sequence of Varnavski, because Varnavski teaches an added, conferred benefit of improved cleavage and expression of heterologous genes such as GFPs in flavivirus constructs. Further, the Office Action asserts that one of ordinary skill in the art would have had a reasonable expectation of success for using the construct of Hurrelbrink, Xiang, Puri, Yamshchikov, and Mishin in view of Zhu with the autoprotease of Varnavski because both Hurrelbrink, Xiang, Puri, Yamshchikov, Mishin, and Varnavski teach construction and expression of flaviviral constructs.

The Office Action further alleges that Chambers teaches flavivirus cDNA backbones (here, JEV) wherein structural proteins are deleted and replaced with proteins of other flaviviruses (nonetheless teaching deletions of structural envelope proteins); with T3 promoters (here the promoter is asserted to be functionally equivalent to T7 promoter) as well as cells comprising them. Barrett is cited for teaching the applicability to WNV as well as structural

similarity among flaviviruses. Further, that Chambers supported by Barrett does not teach WNV lineage I or GFP, but that Hurrelbrink, Xiang, Puri, Friebe, Yamschchikov, and Mishin in view of Zhu indicate construction of flavivirus cDNAs. Moreover, the Office Action asserts that one of ordinary skill in the art at the time the invention was made would have been motivated to construct a full length WN lineage I cDNA with envelope deletions because Chambers teaches flavivirus cDNA backbones comprising envelope deletions for insertion and incorporation of structural proteins, high attenuation and high immunogenicity; Hurrelbrink, Xiang, Puri, Friebe, and Mishin in view of Zhu all teach flavivirus infectious full length cDNA and Barrett teaches the Chambers technology for WN vaccine use. The Office Action also asserts that one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success to construct a full length WN lineage I cDNA comprising envelope deletions because Chambers, Hurrelbrink, Xiang, Puri, Friebe, and Mishin in view of Zhu all teach flavivirus infectious full length cDNA and Barrett teaches the technology for use in structurally similar flaviviruses.

The Office Action further alleges that Varnavski teaches flavivirus (Kunjin) subgenomic replicons, a reverse genetics system; from corresponding plasmids; a reporter gene (GFP); viral promoters (here, SP6; however the promoter is asserted to be functionally equivalent); as well as the autoprotease 2A sequence of FMD. Further, although Varnavski does not teach a WNV lineage I replicon or incorporation of IRES, Pang teaches flavivirus Dengue replicons; Khromykh teaches flavivirus Kunjin replicons and close structural relation with other flaviviruses; Friebe teaches flavivirus HCV replicons; Yamschikov teaches WN lineage II replicons. The Office Action further asserts that Friebe also teaches that incorporation of the IRES in flavivirus RNA enhances direct binding of the 40S ribosome subunit in the absence of additional translation factors. The Office Action asserts that one of skill in the art at the time the invention was made would have been motivated to construct a WN lineage I replicon with an additional IRES element because Varnavski, Pang, Khromykh and Friebe all teach flavivirus replicons (Yamshchikov further teaching WN virus replicons), Khromyke teaches close relation, and Friebe teaches that incorporation of the IRES RNA sequence confers added benefit by enhancing translation. The Office Action further asserts that one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for constructing WN lineage I replicon with an additional IRES element because Varnavski, Pang,

Khromykh, Friebe, and Yamshchikov all teach flavivirus replicons and Khromykh teaches structural similarity among the closely related viruses.

The Office Action further alleges that although Varnavski in view of Pang, Khromykh, Friebe, and Yamschikov in further view of Zhu, do not teach a second reporter or incorporation of IRES, one of ordinary skill in the art at the time of the invention would have been motivated to construct a WN lineage I replicon comprising a second reporter and IRES because Varnavski, Pang, Khromykh and Friebe all teach flavivirus replicons (Yamshchikov further teaching WN virus replicons), Khromykh teaches close relation, and because Zhu teaches enhanced detection for constructs transfected into cells. Furthermore, the Office Action asserts that one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success to construct a WN lineage I replicon comprising a second reporter and IRES because Varnavski, Pang, Khromykh, Friebe, and Yamshchikov all teach flavivirus replicons and Zhu teaches expression of constructs in cells.

Applicants disagree. None of the cited references either alone or in any combination render the instant invention obvious.

None of the cited references relates to the **lineage I WNV** of the present invention. Hurrelbrink relates to plasmids with a genome length cDNA sequence corresponding to *Murray Valley virus*. Xiang relates to construction of a full-length cDNA clone corresponding to *hepatitis G virus*. Puri, relates to a full-length cDNA clone of *dengue 1 Western Pacific*. Yamshchikov relates to a full-length infectious clone of the ***lineage II WN strain***. Mishin relates to *Japanese encephalitis virus*. Friebe relates to sequences important for translation and replication of *hepatitis C virus*. Varnavski relates to replicons of the flavivirus *Kunjin* for expression and delivery of heterologous genes. Pang relates to replicons of *Dengue virus type 2*. This genetic variation between the present invention and the cited references makes it difficult, if not impossible, to predict the outcome of Applicants' invention, namely a reverse genetics system comprising a full-length lineage I WNV cDNA clone.

In particular, Applicants assert that it is well known to one of skill in the art, that there are many difficulties encountered during flaviviral cloning. For example, Shi (copy enclosed) points out on page 5847, first full paragraph:

Infectious full-length cDNA clones for a number of flaviviruses have been successfully developed for the study of viral replication and pathogenesis. In several cases, assembly of full-length

flavivirus clones in a plasmid vector was not straightforward because clones containing large portions of the genome were unstable and deleterious for bacterial hosts.

And, Bredenbeek (copy enclosed) reports¹:

Attempts to construct a stable, full-length infectious YF cDNA in E. coli plasmid and λ phage vectors have been unsuccessful due [to] problems with the genetic stability of the full-length clone in the prokaryotic host.

And, Mishin reports on page 120, right column, that:

the “Design of flavivirus ‘infectious DNA’, however, has proven to be a more challenging task, perhaps due to the *well known instability of plasmids carrying flavivirus genome cDNA*”.

Moreover, this reference reports that attempts to assemble full JE genome cDNA under control of the CMV promoter were unsuccessful; that a half genome cassette containing JE structural proteins was also extremely unstable; and that similar instability problems were encountered with JE constructs driven by the Rous sarcoma virus (RSV) long terminal repeat.

Furthermore, Mishin highlights that the difficulties associated with achieving transcription involve various factors including manipulation of the reporter construct, the promoter, the bacterial or cellular system used to achieve replication and their regulatory elements (see page 120, right column to page 121, left column).

Thus it is respectfully submitted that one of skill in the art would expect that ANY insertions, deletions, or variations in the genome of a flavivirus may create difficulties with expression, stability, or infectivity of resultant RNA in a reverse genetics system, and that it is therefore inappropriate to extrapolate the construction of one flavivirus to another. These references make it clear that one of skill in the art would have no expectation of successfully practicing the present invention. The claimed invention is **more** than the predictable use of prior-art elements according to their established functions.

For the reasons above, Hurrelbrink, Xiang, Puri, Yamshchikov, Mishin, Friebe, Varnavski, and Pang cannot be said to teach or suggest the present invention. The Examiner is again respectfully reminded that a reference used in a prior art rejection must contain an enabling disclosure. *In re Hoeksema*, 399 F.2d 269, 273 (C.C.P.A. 1968). And, that BOTH the

¹ Bredenbeek, PJ, Kooi, EA, Lindenbach, B, Huijckman, N, Rice, CM, and Spaan, WJM: A stable full-length yellow fever virus cDNA clone and the role of conserved RNA elements in flavivirus replication. J. Gen. Vir. (2003) 84: 1261-1268, at 1262, (citing Rice *et al.*, 1989).

suggestion of an invention, and a reasonable expectation of success must be found in the prior art, i.e., “obvious to try” is not the test. Here, the cited references all fail the test by NEVER successfully teaching the full-length lineage I WNV cDNA clone of the present invention.

Furthermore, Applicants remind the Examiner that it is impermissible to engage in a hindsight reconstruction of the claimed invention, using the Applicant’s structure as a template, and selecting elements from references to fill in the gaps. *Interconnect Planning*, 744 F.2d 1132, 1143 (Fed. Cir. 1985). Applicant believes that only through the exercise of impermissible hindsight have the cited references been selected and relied upon by the Office. There is no teaching or suggestion in the cited art to motivate one of ordinary skill in the art to combine elements of the references to result in the presently claimed invention. Simply, there was no apparent reason to combine the known elements in the fashion claimed by the patent at issue.

Consequently, reconsideration and withdrawal of the Section 103 rejections are earnestly requested.

REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, a further interview with the Examiner and SPE are respectfully requested and the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

Reconsideration and withdrawal, or modification of the restriction requirement, and a prompt and favorable examination on the merits, is respectfully requested.

Respectfully submitted,

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